Sacral nerve stimulation reduces elevated urinary nerve growth factor levels in women with symptomatic detrusor overactivity

Dara Faye Shalom, MD; Nirmala Pillalamarri, MD; Xiangying Xue, MD; Nina Kohn, MBA, MA; Lawrence Russell Lind, MD; Harvey Allen Winkler, MD; Christine Noel Metz, PhD

OBJECTIVES: To investigate changes in urinary nerve growth factor (uNGF) in women with symptomatic detrusor overactivity (DO) following peripheral nerve evaluation (PNE) for sacral neuromodulation vs controls.

STUDY DESIGN: There were 23 subjects with overactive bladder symptoms and DO who failed management with anticholinergics and 22 controls consented to participate in this prospective pilot study. Urine specimens were collected from controls at baseline for evaluation of uNGF and creatinine. Subjects were evaluated at baseline and 5 days after a trial of sacral nerve stimulation referred to as a PNE. Each visit included urine collection for uNGF and, Incontinence Quality of Life Questionnaire, Urinary Distress Inventory Questionnaire, postvoid residual volume, and a 3-day voiding diary. uNGF levels were measured by enzyme-linked immunosorbent assay and expressed as uNGF pg/creatinine mg.

RESULTS: Subjects with DO had significantly higher baseline uNGF levels (corrected for creatinine) compared with controls (19.82 pg/mg vs 7.88 pg/mg, $P < .002$). Seventeen DO subjects underwent PNE and were evaluated at the end of the testing period. There was a significant improvement in quality of life scores for subjects after PNE compared with baseline (Urinary Distress Inventory Questionnaire: 7.0 vs 13.7, $P < .001$; Incontinence Quality of Life Questionnaire: 87.3 vs 52.8, $P < .0001$). Concordantly, uNGF levels significantly decreased from 17.23 pg/mg to 9.24 pg/mg ($P < .02$) after PNE.

CONCLUSION: uNGF levels decrease with symptomatic response in DO subjects undergoing PNE. DO subjects had significantly higher uNGF at baseline vs controls, and uNGF levels significantly decreased after only 5 days of sacral nerve stimulation. These findings support a larger study to validate the use of uNGF as an objective tool to assess therapeutic outcome in patients undergoing PNE for sacral neuromodulation.

Key words: detrusor overactivity (DO), overactive bladder (OAB), sacral neuromodulation, urinary nerve growth factor (uNGF)

Cite this article as: Shalom DF, Pillalamarri N, Xue X, et al. Sacral nerve stimulation reduces elevated urinary nerve growth factor levels in women with symptomatic detrusor overactivity. Am J Obstet Gynecol 2014;211:561.e1-5.

Overactive bladder (OAB) is a condition often characterized by disabling symptoms of urinary urgency and frequency with or without urge incontinence. Detrusor overactivity (DO) can be a cause of OAB and is diagnosed when involuntary detrusor contractions are noted during the filling phase of urodynamic testing. OAB is common, with an estimated prevalence of 16% in women in the United States, and is known to adversely affect quality of life.[1,2] Treatment options for patients with OAB have expanded throughout the past decade. In patients who are refractory to first-line treatment with behavioral modifications and anticholinergics, sacral neuromodulation can be offered. This therapy is unique in that a trial phase, referred to as a peripheral nerve evaluation (PNE), is performed in order to determine whether patients will respond to therapy. During PNE, patients receive 3-5 days of sacral nerve stimulation via a temporary test stimulation lead placed in the S3 foramina. The decision to proceed with permanent implantation of the sacral neuromodulation device, the implantable pulse generator, is based primarily on voiding diary results. A patient meets criteria for implantation if they experience a 50% decrease in the number of voids and/or leakage episodes during the testing phase.

Nerve growth factor (NGF) is a small secreted protein that promotes differentiation and survival of target neurons. NGF is produced in the bladder and is reported to sensitize afferent nerves and induce bladder overactivity.[3] This

From the Division of Female Pelvic Medicine and Reconstructive Surgery, Department of Obstetrics and Gynecology (Drs Shalom, Pillalamarri, Lind, and Winkler), North Shore—Long Island Jewish Health System, Great Neck, and the Center for Immunology and Inflammation, The Feinstein Institute for Medical Research (Drs Xue and Metz), and Biostatistics Unit, Feinstein Institute for Medical Research (Ms Kohn and Dr Metz), Manhasset, NY.

Received March 10, 2014; revised June 6, 2014; accepted June 23, 2014.

L.R.L. is a consultant for Boston Scientific. The remaining authors report no conflict of interest.

This research was supported by a grant from Medtronic Inc, Minneapolis, MN (D.F.S.).

Presented in oral format at the 40th Annual Scientific Meeting of the Society of Gynecologic Surgeons, Scottsdale, AZ, March 23-26, 2014.

Corresponding author: Nirmala Pillalamarri, MD. npillalama@nshs.edu

0002-9378/$36.00 • http://dx.doi.org/10.1016/j.ajog.2014.07.007

bladder overactivity is linked to mechanical stretch and reflex bladder muscle activity.[3] NGF has been identified in the bladder urothelium, bladder smooth muscle, and urine of patients with OAB.[3-5] Recent studies have demonstrated that levels of urinary NGF (uNGF) correlate with patient reported bladder symptoms[3-6] and may decrease following successful treatment.[3,4,6,7]

The cause of OAB remains unclear, and currently disease severity and response to treatment is assessed through patient report. The lack of a standardized noninvasive objective test to evaluate disease progression and response to treatment makes the evaluation of patients with OAB exceedingly difficult. It has been established that NGF is elevated in the urine of patients with OAB and DO, and has been shown to decrease in patients who have a symptomatic response to therapy.[3-7] We aim to confirm this finding in our patient population and to investigate the use of NGF as a potential biomarker for evaluating symptomatic response in patients undergoing PNE for sacral neuromodulation. Our hypothesis is that OAB patients with DO will have elevated NGF levels as compared with controls and that the level of NGF will decrease in patients who have symptomatic improvement following PNE.

Materials and Methods

Subjects and study design

This prospective case–control study was approved by the institutional review board of the North Shore–Long Island Jewish Health System (#11-060A) before its initiation. This is a pilot study conducted to assess the change in uNGF levels in DO patients after sacral nerve stimulation. All subjects (women) gave written informed consent before study procedures. Subjects (cases and controls) were recruited from the urogynecology practice of the North Shore–Long Island Jewish Health System between Aug. 11, 2011, until March 13, 2013. Cases were enrolled in the study if they had OAB symptoms including urinary frequency, urgency or urge incontinence for greater than 3 months, a urodynamic diagnosis of DO, and experienced no improvement following treatment with anticholinergics and behavioral modifications. Controls were age-matched (±5 years), and denied symptoms of urinary frequency, urgency, or incontinence. Exclusion criteria for both cases and controls included: presence of acute cystitis (confirmed by positive urine culture), urinary tract tumors or stones, bladder outlet obstruction, postvoid residual (PVR) volume >100 mL, history of urinary tract operation (including urogynecologic procedures such as slings) within 6 months, history of intravesical botox usage within 1 year, interstitial cystitis, neurologic disorder, and use of anticholinergics within the past 21 days.

At baseline, a clean-catch urine specimen was collected from all controls for determination of uNGF and creatinine (Cr) levels. All cases completed a 3-day voiding diary, Incontinence Quality of Life Questionnaire (I-QOL) and the Urinary Distress Inventory Questionnaire (UDI-6) at baseline. The I-QOL is a validated 22-item quality of life instrument specific to urinary incontinence.[8] Higher scores indicate a better quality of life. The UDI-6 is a validated 6-item questionnaire specific to incontinence in which higher scores indicate worse symptoms.[9] A clean-catch midstream urine specimen was collected for determination of uNGF and Cr levels, and a PVR volume was measured with a bladder ultrasound. Cases then underwent a 5-day PNE whereby an electrode (Model 3057 Test Stimulation Lead; Medtronic Inc, Minneapolis, MN) was placed into a unilateral S3 foramen under fluoroscopic guidance. The technique of the PNE has been described previously.[10] Proper S3 lead placement was confirmed by fluoroscopy as well as patient sensation of stimulation and direct observation of plantar flexion of the great toe using the external test stimulator (InterStim, Medtronic Inc). The test stimulation lead was then placed into the test stimulation cable and test stimulator (Model 3625; Medtronic Inc). The external handheld test stimulator was adjusted to achieve an optimum level of sensation, and instructions on using the test stimulator were given. Cases then began a 5-day trial of sacral nerve stimulation. A voiding diary was completed each day of the PNE trial. After 5 days, cases returned to the office for follow-up and lead removal. The follow-up visit included collection of a clean-catch urine specimen followed by determination of PVR (as described above), and completion of the I-QOL and UDI-6.

Urine processing and uNGF and serum creatinine determinations

Urine samples were centrifuged within 3 hours of collection at 3000 g for 10 minutes. The liquid supernatant was separated into 1.5 mL aliquots and stored at −80° C. uNGF (performed in triplicate) levels were measured using a specific and highly sensitive enzyme-linked immunosorbent assay method (Emax; Promega, Madison, WI), according to the manufacturer's suggestions. Prior studies on uNGF reported results using the same enzyme-linked immunosorbent assay kit for reproducibility.[11] Sample concentrations were determined by extrapolating from the uNGF standard curve. Urinary creatinine levels were determined using the enzymatic creatinine assay (Diazyme Laboratories, Poway, CA), according to the manufacturer's directions. Total uNGF levels (pg/mL) were normalized by urinary creatinine to overcome differing dilutions of urine between subjects. Data are presented as: mean (uNGF [pg]/Cr [mg]) ± SD.

Statistical analyses

Comparisons between groups (cases vs controls) for uNGF/Cr levels were made using the Mann–Whitney test. Change in number of leaks and voids per day, uNGF/Cr levels, and quality of life measures before and after PNE were compared in DO subjects using the Wilcoxon signed-rank test. P values $< .05$ were considered significant.

Results

Characteristics of the study population

A total of 23 female subjects with OAB symptoms and urodynamically proven DO met inclusion criteria and were